role of apoptosis during early brain morphogenesis is to ensure the completion of neural tube closure.

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Program/Abstract # 86
Sprouty genes function as negative regulators of the FGF signalling pathway during cerebellar development
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The cerebellum is derived from dorsal rhombomere 1 in the embryo. Previous studies have demonstrated the importance of FGF signals for the maintenance and patterning of r1 in the early embryo. Three Sprouty genes (Spry1, Spry2 and Spry4), which encode feedback antagonists of FGF signalling, are expressed in the mid-hindbrain (MH) organiser and MH-specific Spry1;2 and Spry1;2;4 knockout embryos exhibit enlarged cerebellar primordia (r1) due to increased FGF signalling. We also observed FGF and Sprouty gene expression during later stages of cerebellar development, implying roles for these genes in precursors of various cerebellar cell types such as Bergmann glia, granule and Purkinje neurons. In support of this idea, MH-specific Spry1;2 and Spry1;2;4 knockout cerebella analysed at postnatal day (P)21 have fewer granule neurons and abnormal foliation. The expression of FGF target genes, Pea3 and Erm are increased, and SHH target genes, Gli1 and Ptch1 are decreased in P7 mutant cerebella. The phenotype of Sprouty mutant can be rescued by reducing FGF receptor 1 and Ptch1 gene dosage, providing genetic proof that the cerebellar defects in Sprouty knockouts are due to deregulated FGF and SHH signalling. Cell type-specific conditional gene knockout experiments suggest that Sprouty gene function is required in several cerebellar cell types during development.

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Program/Abstract # 87
LRP2/megalin is required for the FGF-dependent expansion of the basal telencephalon
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Loss of endocytic receptor LRP2/megalin in mice impairs specification of the developing CNS, leading to holoprosencephaly. This phenotype results from impaired morphogen signaling in the early rostral forebrain organizer indicating an important function for LRP2 in neurulation (see abstract by Annabel Christ). Since expression of *Lrp2* persists throughout embryonic development, we wanted to test whether the receptor may also have additional functions in later stages of brain formation. Employing *Foxg1*^{cre}-mediated conditional recombination, we generated mice lacking LRP2 in the telencephalon from embryonic day 9.5 onwards. Conditional *Lrp2* mutants showed a reduced thickness of the basal telencephalon and an expansion of the telencephalic vesicles. We did not observe loss of distinct differentiated cell types but an overall reduced proliferation in the ventral telencephalon. The rate of apoptosis was unchanged. Remarkably, loss of LRP2 after neurulation in the embryonic telencephalon did not affect the SHH or BMP4 pathways, which are severely compromised in constitutive *Lrp2* mutants. Rather, conditional LRP2 deficiency specifically exhibited dorsal expansion of *Fgf8* and *Fgf17* gene expression domains in the rostral forebrain. FGF signaling has been previously implicated in the regulation of proliferation in rostroventral telencephalon. We thus identified a late developmental role for LRP2 in maintaining proliferation and correct expansion of the basal telencephalon, likely mediated by FGF signaling.

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Program/Abstract # 88
Disruption of Apaf1 leads to defective craniofacial development in the mouse embryo
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Using a mouse strain isolated during an ethyl-nitrosourea (ENU) screen for recessive point mutations affecting midgestation morphology, we identified a role for apoptotic peptidase activating factor 1 (*Apaf1*) during craniofacial development. *Apaf1* is a key component of the mitochondria-mediated apoptotic pathway, functioning upstream of caspases 9 and 3. Interestingly, mice lacking caspase 9 or 3 do not exhibit craniofacial defects in their phenotypes, demonstrating a novel contribution of *Apaf1* to facial development. Twenty percent of our mutant mice show craniofacial abnormalities (wide frontonasal prominence, cleft face, short/broad nasal region) by embryonic day 12.5. We observe these defects as early as embryonic day 10; they vary in severity, and persist until birth – at which point we see skull defects (in the frontal, nasal, and maxilla/premaxilla bones). Our mutant allele is due to a T to C transition in exon 8 of *Apaf1*, resulting in a proline substitution at a highly conserved leucine (L375P). We found this is a critical residue as protein levels are unaffected in our mutants. Furthermore, our Apaf1 allele phenocopies targeted *Apaf1*-null alleles and fails to complement a spontaneous mutant that is functionally deficient in *Apaf1*. Taken together our analyses of this novel allele of Apaf1 identify a previously unrecognized residue that is important for *Apaf1* function, and provide evidence for a caspase-independent role of *Apaf1*.

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Program/Abstract # 89

ABSTRACT WITHDRAWN

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Program/Abstract # 90
Aglossia in Hand2 conditional knockout mutants results from misregulation of Dlx5/6
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The development of the lower jaw is regulated spatiotemporally by signaling cascades, and is refined through both permissive and inhibitory signals. We have shown that endothelin-A receptor (Ednra) signaling is a central regulator of lower jaw identity, establishing the identity of cranial neural crest cells (NCCs) in the mandibular arch through a mechanism involving *Dlx5* and *Dlx6*